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Characterization of the Metabolically Healthy Phenotype in Overweight and Obese British Men

LEE INGLE[1*] PhD FESC; MICHELLE MELLIS2 PhD; DAVID BRODIE[3] PhD; GAVIN R SANDERCOCK[4] PhD

***Address for correspondence**

[1]*Department of Sport, Health & Exercise Science*

University of Hull

Hull

United Kingdom

Tel: 01482 463141

Email: L.Ingle@hull.ac.uk

2Carnegie Faculty, Leeds Beckett University, Leeds, UK

[3]*Department of Health, Buckinghamshire New University, Bucks. UK*

[4]*Centre for Sport & Exercise Science, University of Essex, Essex, UK*

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Abstract:

We calculated the prevalence of the metabolically healthy but obese (MHO) phenotype in (n=9 177) British men (age 48.9±7.4 years) attending preventive health screening between 2000 and 2009. We examined differences in cardiorespiratory fitness (Fitness) and self-reported physical activity levels, according to whether the men were metabolically healthy (<2 components of the metabolic syndrome), and by BMI category (normal-weight, over-weight, obese). Fitness was estimated from treadmill exercise as VO_{2peak} and classified as: Low, Moderate, or High using age-specific cut-offs. We identified 21.6% of our sample as obese, of whom 83.1% were metabolically healthy. Compared with the metabolic unhealthy obese (MUO; 3.7% of sample), MHO phenotypes were fitter (effect size d=0.21) and were more physically active (d=0.31). Logistic regression showed high fitness (OR=2.40, 95%CI 1.38-4.19), and being physically active (OR=1.71, 95% CI 1.14-2.56) to be independently associated with the MHO phenotype. Our findings agree with US data suggesting that higher cardiorespiratory fitness is a characteristic of the MHO phenotype. Our finding that meeting physical activity guidelines was associated with the MHO phenotype independent of fitness is, however, novel. If confirmed, our findings indicate that public health messages that en-courage active lifestyles to promote fitness should be encouraged regardless of weight status.

Introduction:

Individuals with an adverse metabolic health profile have a three-fold greater risk of all-cause mortality than those who are metabolically healthy, regardless of their body mass index (BMI) (Kramer et al., 2013). This reduced mortality risk is greatest in obese individuals who remain metabolically healthy (Kramer et al., 2013; Roberson et al., 2014). Attempts to characterize the metabolically healthy obese (MHO) phenotype suggest they are younger and have a more favorable body fat distribution than metabolically unhealthy obese (MUO) individuals (Primeau et al., 2011). Visceral fat accumulation, birth weight, and adipose cell size have been implicated in the development of the MHO phenotype, but the authors did not explore the potential roles of physical activity or cardiorespiratory fitness (fitness).

A review of possible factors underlying the lower mortality risk associated with the MHO phenotype (Roberson et al., 2014) identified seven studies showing they were more active than MUO individuals. Roberson et al. (2014) identified one study (Katzmarzyk et al., 2005) which reported that differences in fitness accounted for the increased risk of cardiovascular mortality observed in MUO phenotypes, compared with normal-weight individuals of normal-weight (MHNw). Based on these findings, Roberson and colleagues[12] suggested that all studies examining the MHO phenotype should assess physical activity or fitness due to their possible mediating effect on cardiovascular disease risk. Another recent review characterizing the role of fitness in the MHO phenotype identified ten studies reporting higher fitness in MHO compared with MUO phenotypes (Ortega et al., 2015). Findings were mostly limited to comparisons between small groups of post-menopausal women. However, a recent, larger study of >5 000 US men and women (Ortega et al., 2013) also found significantly higher fitness in MHO versus MUO phenotypes. Ortega et al (2015) suggested that such findings may help inform public health messages that emphasise the importance of tackling low fitness as well as weight loss *per se*. The cardio-protective effects of physical activity (Blair and Jackson, 2001) and fitness (Aspenes et al., 2011) independent of adiposity (Lee et al., 2012) are well documented, yet fitness remains an underused and underrated prognosticator (Mark and Lauer, 2003; Roger et al., 1998).

To evaluate this proposal, we aimed to undertake a detailed examination of differences in physical activity and fitness across groups defined by metabolic health and BMI status. Using criterion referenced standards for fitness and physical activity we also sought to clarify the relative contribution of physical activity and fitness to metabolic health within and across different BMI categories.

Methods:

Ethical approval was granted by the Faculty of Society & Health ethics committee, Buckinghamshire New University. Men (aged 20-69 years) attended one of five Health & Wellbeing clinics around England for a three-hour preventative health assessment between 2000 and 2009. Participants attended general health examinations as an annual benefit provided by their corporate wellness schemes. Screening attendance was voluntary, as such the study participants represent a self-selected opportunity sample. Each participant was instructed in their pre-assessment information pack to avoid vigorous physical activity, alcohol and caffeinated beverages for 24 hours prior to their assessment. Participants, in a supine position, underwent a resting electrocardiogram (ECG) for 5 min using the Marquette CASE Stress system (GE Healthcare, UK). Each participant signed and consented to the test battery which was countersigned by the duty medical officer.

Demographic and anthropometric measurements

Participants reported their date of birth, and home postcode. Date of birth was used to calculate age, and postcode was used to determine area-level deprivation using the English Indices of Deprivation (EID)[20].

Body mass was measured using digital scales (Marsden Weighing, Rotherham, UK) and recorded to the nearest 0.1 kg. Clothing was worn but shoes and belts were removed, and participants evacuated their bladder before stepping onto the scales. Scales were calibrated daily with a known weight and bi-annually by the manufacturer. Stature was measured using a stadiometer (Seca, Hamburg, Germany) and recorded to the nearest 0.1 cm. Participants removed their shoes, stood on the platform with feet together, and head in the Frankfort plane. Buttocks and scapulae were in contact with the back of the stadiometer, shoulders relaxed with hands and arms loosely at the sides, the measurement was taken on full inhalation. Body mass index (BMI, $kg \cdot m^{-2}$) was calculated and categorized as normal-weight (18.5-24.9 $kg \cdot m^{-2}$), overweight (25-29.9 $kg \cdot m^{-2}$) or obese ($\geq$30 $kg \cdot m^{-2}$). Waist circumference (WC) was measured to the nearest 0.1 cm using a flexible anthropometric tape measure, midway between the lowest rib and the iliac crest at minimal inspiration.

Participants reported the frequency of moderate weekly bouts of physical activity (e.g. at least 30 min of brisk walking) and vigorous sessions per week (e.g. at least 20 min of gym or sporting activity). Participants were categorized as physically active if they achieved ≥150 min of moderate activity or 75 $min \cdot week^{-1}$ vigorous activity per week. Participants also self-reported whether they smoked tobacco or drank alcohol and if so, how many units they consumed in a typical week.

Venous blood sampling

Participants presented in a fasted state (for the previous 12 hours) but ate a snack (fruit or muesli bar) prior to the exercise test. At the start of each assessment, fasted venous blood samples were obtained using vacutainer tubes and heparinised whole blood was analysed using the Piccolo blood chemistry analyser (Abaxis, USA). The following analytes were measured: glucose, total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), tryglycerides, and TC/HDL ratio.

Exercise tolerance test

Participants positioned themselves on the T2100 treadmill (GE Healthcare, UK), and undertook an incremental exercise test using the Bruce protocol. Blood pressure was monitored at the second minute of each stage using the automatic Tango stress test BP monitor (Suntech Medical, Oxfordshire, UK). Ratings of Perceived Exertion were recorded at the end of each stage using the 6-20 Borg Scale. The ECG was monitored throughout the test. Participants exercised until they attained ≥85% of age-predicted maximum heart rate (220-age) or met any of the test termination criteria outlined by the American College of Sports Medicine (ACSM, 2013). VO_{2peak} was estimated and reported in $ml \cdot kg^{-1} \cdot min^{-1}$.

Data treatment

We excluded participants with a BMI <18.5 $kg \cdot m^{-2}$ and >40 $kg \cdot m^{-2}$, and those diagnosed with diabetes mellitus, coronary artery disease, or cancer.

We classified participants as metabolic healthy if they presented with <2 components of the metabolic syndrome (MetS) excluding waist circumference (Ortega et al., 2015; Ortega et al., 2013; Primeau et al., 2011; Roberson et al., 2014). The four components assessed were: blood pressure >130/85 mmHg, HDL cholesterol <1.036 $mmol\cdot l^{-1}$, triglycerides >1.695 $mmol\cdot l^{-1}$ and fasting plasma glucose >6.1 $mmol\cdot l^{-1}$ (Grundy et al., 2005). Data were divided into 10-year age strata and VO_{2peak} ($ml\cdot kg^{-1}\cdot min^{-1}$) was categorized as low (≤20th percentile), moderate (>20-<80th percentile) or high (≥80th percentile) fitness based on age-specific reference values (Heyward, 2014).

Data Analysis

We cross-tabulated metabolic health and BMI to create six phenotype groups: Metabolically Healthy Normal-weight (MHNw), Metabolically Unhealthy Normal weight (MUNw), Metabolically Unhealthy Overweight (MUOw), Metabolically Healthy Overweight (MUOw), Metabolically Unhealthy Obese (MUO), and finally, Metabolically Healthy Obese (MHO). We examined between-phenotype differences in fitness and physical activity using two-way analysis of variance (ANOVA). If there was a significant main effect for metabolic health, between metabolically healthy and unhealthy groups we also calculated effect sizes (Cohen's d). Pearson's χ^2 tests were used to compare categorical variables across BMI categories and groups. Separate χ^2 tests were used to examine frequency differences within BMI categories.

Within each BMI category, multivariate logistic regression was used to calculate the age-adjusted odds of being metabolically healthy according to physical activity (active) and fitness (moderate, high). We first calculated age-adjusted OR of good metabolic health within Model 1.We then adjusted estimates of age, smoking status, alcohol consumption and BMI (continuous variable; Model 2). Finally, to account for the effects of central adiposity, we calculated a fully-adjusted model including waist circumference (Model 3). Collinearity diagnostics were performed to calculate tolerance and variance inflation factors (VIF); multicollinearity requiring was defined as a VIF>4 and serious (requiring correction) if VIF>10.   .

To assess whether associations between fitness, physical activity, and metabolic health were independent of BMI category, we calculated age-adjusted ORs of MH according to: Fitness (High, Moderate or Low), self-reported physical activity (Active or Inactive), and BMI category (NW, Ow, O). We next adjusted this model for age, smoking status and alcohol consumption (Model 2) then additionally for WC (continuous; Model 3) .. All analyses were performed in SPSS version 22.0 (SPSS an IBM Company, IBM Ltd. NY, USA) was used to analyze all data.

Results

We recruited n=9177 men (age 48.9±7.4 years) of whom 56.4% were overweight and 21.6% were obese (Table 1). Overall, 84.2% of participants were classified as metabolically healthy but this was less common in those who were obese (83.1%) compared with overweight or normal-weight. The MHO phenotype accounted for 17% of the total sample.

Differences within BMI categories according to metabolic health

Mean VO_2peak was significantly higher in the MHO phenotype (37.9±9.0) compared to the MUO phenotype (36.0±8.9; d=0.21), as were self-reported levels of physical activity (d=0.31) Mean weekly minutes MVPA was significantly higher in the MHOw compared with the MUOw phenotype.(d=0.21

Associations between Fitness, Physical Activity and Metabolic Health within BMI categories.

Table 2 shows the results from logistic regression analyses performed separately by BMI category. Age-adjusted odds ratio show that obese men, who were moderately or highly fit, and those who were physically active, were more likely to be metabolically healthy (MHO phenotype). These associations remained significant when adjusting for smoking status, alcohol intake, and BMI ($Model_2$).

In obese men, being moderately or highly fit, and being physically active, was positively associated with metabolic health (Models 1 and 2, Table 2). While adjusting for waist circumference, abrogated the association between moderate fitness and metabolic health; being highly fit and physically active retained the independent association with metabolic health.

Overweight men who were physically active, and moderately or highly fit, were more likely to be metabolically healthy. The associations between metabolic health and fitness were independent of BMI, smoking status, alcohol consumption (Model2) and waist circumference (Model3). Normal weight men were more likely to be metabolically healthy if they were highly fit and physically active. These independent associations remained important in Model2 and, after further adjustment for waist circumference (Model3).

Associations of Metabolic Health with Fitness, Physical Activity and BMI category

Table 3 provides results from multivariate logistic regression analyses in all participants demonstrating associations between BMI (categories), physical activity, and fitness categories and metabolic health. The adjusted (Model2) analyses showed men who were moderately (OR=1.21, 95%CI: 0.98-1.51), or highly fit (OR=1.84, 95%CI: 1.44-2.35), and those who were physically active (OR=1.71, 95%CI: 1.14-2.56) were independently associated with metabolic health. We found no meaningful association between weight status (BMI categories) and metabolic health. In contrast, moderate fitness, high fitness, and being physical active all retained meaningful, independent associations with metabolic health in all models including Model3 which adjusted for waist circumference.

Discussion:

Cardiorespiratory fitness may be an important factor in the favorable prognosis reported in the MHO phenotype (Ortega et al., 2015; Ortega et al., 2013; Roberson et al., 2014). Compared with physical activity (Hamer and Stamatakis, 2012; Hosseinpanah et al., 2011; Katzmarzyk et al., 2005; Roberson et al., 2014) few studies have compared obese men's cardiorespiratory fitness. We sought to characterize the MHO phenotype in terms of cardiorespiratory fitness and physical activity, with and across BMI categories.To expand on previous work we also characterized the metabolically healthy phenotype in normal weight and overweight men. Seventeen percent of the current sample were of the MHO phenotype; comparable with data reported by Ortega et al. (2013) who used the same criteria in US men. Comparisons between populations are problematic as MHO is dependent on both the prevalence of obesity and the metabolic health of the population. The proportion of our sample classified as obese is comparable with the prevalence (23.8%) in a previous study of British adults[5]

Across all BMI categories, those who were metabolically healthy were also significantly fitter and more physically active, but the largest differences were evident in obese men. These findings are in agreement with reported differences in physical activity levels (Wildman et al., 2005) and fitness (Ortega et al., 2013) in US men. We also identified higher fitness and meeting physical activity guidelines as independent predictors of metabolic health across all three BMI groups. In the NHANES III update, Wildman et al. (2008) reported higher physical activity levels in MHO and MHOw phenotypes compared with obese overweight adults with poor metabolic health. Achieving recommended MVPA (through moderate or vigorous activity) had little effect on mortality risk if fitness was low. Indeed, a higher degree of fitness is protective whether or not physical activity recommendations are followed.[23]

It appears, therefore, that higher physical activity levels and better cardiorespiratory fitness are two characteristics of the MHO phenotype; both may explain the longevity and reduced morbidity frequently reported in MHO, compared with individuals with the MUO phenotype. Surprisingly, few large population-based studies have examined the possible role of fitness and physical activity in the MHOw and MHO phenotype; in a systematic review, Primeau et al. (2011) made no mention of physical fitness. Ortega et al. (2013) found fitness-adjusted mortality risk was 30-50% lower in the MHO compared with MUO phenotypes. They concluded that obesity was a benign condition in the MHO phenotype with good cardiorespiratory fitness. These data concur with recent reviews suggesting that cardiorespiratory fitness plays an important role in maintaining good metabolic irrespective of and individual's weight status (Kramer et al 2013; Lee et al 2012; Ingle et al 2016).

To our knowledge, previous studies have not examined differences in physical activity and fitness across all six phenotypes. Our findings highlight that both MHOw and MHO phentoypes had levels of physical activity and cardiorespiratory fitness broadly comparable with normal-weight men. Ortega et al. (2013) proposed fitness was a characteristic of MHO individuals which may go some way to explaining the high prevalence of the MHO phenotype in the present cohort. Just as evidence for the 'fat but fit' phenotype (Lee et al., 2005) challenged assumptions that these characteristics were mutually exclusive, our findings challenge the assumption that individuals have an inevitably higher risk of metabolic ill-health based solely on evidence of raised BMI value. Conversely, as normal–weight men with poor metabolic health comprised a comparable proportion of the total sample (3.3%) to MUOs (3.7%) these findings also contradict the assumption that a 'normal' BMI (sometimes referred to as a healthy BMI) is indicative of good metabolic health.

Within all BMI categories we found evidence for a dose-response between metabolic health and fitness. Even in our fully-adjusted models, obese men with high fitness were more than twice as likely to be metabolically healthy. This association was also evident in overweight and normal-weight men in whom moderate fitness was not a significant predictor of MH. The pattern of these associations between fitness and metabolic health are in agreement with previous investigations of MHO phenotype but also with the evidence-base showing that high adiposity and fitness are not mutually exclusive and that the latter is cardio-protective independent of weight status (Blair and Jackson, 2001; Lee et al., 2011; Wing et al., 2007).

The majority of MHO phenotype studies including assessment of energy expenditure have reported either physical activity (Bobbioni-Harsch et al., 2012; Hamer and Stamatakis, 2012; Hosseinpanah et al., 2011; Katzmarzyk et al., 2005; Kuk and Ardern, 2009; Meigs et al., 2006; Ortega et al., 2013; Song et al., 2007; Voulgari et al., 2011) or fitness (Katzmarzyk et al., 2005; Ortega et al., 2013). While objective measures of cardiorespiratory fitness are more strongly associated with all-cause (Lee et al., 2011) and cardiovascular (Williams, 2001) -related mortality, both constructs are associated with CVD risk (Blair and Jackson, 2001; Earnest et al., 2013; Lee et al., 2011; Williams, 2001). To our knowledge, this is the first study to demonstrate that fitness and physical activity are independently associated with metabolic health in obese men. Importantly, meeting current physical activity guidelines was associated with a 23% greater likelihood of good metabolic health in the most prevalent BMI category (overweight) and in normal-weight (60%) men. We believe this to be the first study to show metabolic health is independently associatedwith physical activity, and cardiorespiratory fitness even when adjusted for both BMI and central adiposity.

BMI, and, to a greater extent, central adiposity, are both associated with metabolic ill-health. Even after controlling for waist circumference (a proxy measure of central adiposity) and BMI categories (Table 3), moderate and high fitness, and being physically active, all remained positively associated with the likelihood of being metabolically healthy The association with physical activity and fitness was independent of one another, suggesting an important role for both, while in contrast, BMI category appeared relatively unimportant. . Despite 78% of participants being classified as either overweight or obese, according to BMI category, the vast majority (83%) of these men were metabolically healthy. These findings suggest that (especially high) levels of fitness and physical activity not only attenuate metabolic risk in obese men (Blair and Jackson, 2001; Wing et al., 2007), but have a much greater potential impact on metabolic health than body size status assessed by BMI.

Limitations

The use of estimated VO_{2peak} is a limitation of the present data but the similarity between our estimated values for fitness and those from similar studies, which have used direct measurement, justify our approach. A limitation of our study is that VO_{2peak} testing protocols during preventative health screening changed in 2006. Prior to 2006, participants performed a maximal exercise test to volitional exhaustion, after which, test termination criteria of achieving ≥85% predicted maximum HR was introduced. Correlating between date of test and VO_{2peak} values revealed a low, positive association ($r<0.10$) indicating that the change in protocol was not associated with systematically lower estimates of fitness. The use of self-report physical activity questionnaires may provide questionable validity and reliability. Measurement error could be inflated due to issues of accurate recall.

Generalizing these findings to the wider population should be made with caution; our sample was mainly derived from regions with below-average levels of deprivation. Lower deprivation is associated with higher health-literacy which is associated with better metabolic health (Walker et al., 2014), higher levels of physical activity (d'Orsi et al., 2014), and an increased likelihood of participating in health screening (Lyratzopoulos et al., 2006). The self- selecting nature of the sample may also explain the low overall prevalence of metabolic ill-health, as those accepting an offer of preventive screening are likely to engage in other healthy behaviors (Lyratzopoulos et al., 2006). It is possible that the relatively high levels of physical activity and associated cardiorespiratory fitness levels may not be reflective of less affluent areas.

In conclusion, the metabolically healthy obese phenotype is relatively common in British men and is characterized by higher levels of cardiorespiratory fitness and meeting current physical activity guidelines.

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